British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **81** 929–940 929

PHARMACOKINETICS

Pharmacokinetics and tolerability of paritaprevir, a direct acting antiviral agent for hepatitis C virus treatment, with and without ritonavir in healthy volunteers

Correspondence Dr Rajeev M. Menon, Senior Director, Clinical Pharmacokinetics and Pharmacodynamics, AbbVie, 1 North Waukegan Road, AP31-3, North Chicago, Illinois 60064, USA. Tel.: +1 847 935 9066; Fax:+1 847 938 5193; E-mail: rajeev.menon@abbvie.com

Received 30 July 2015; **revised** 17 December 2015; **accepted** 21 December 2015

R. M. Menon[1], C. E. Klein[1], T. J. Podsadecki[2], Y.-L. Chiu[3], S. Dutta[1] and W. M. Awni[4]

[1]Clinical Pharmacokinetics and Pharmacodynamics, AbbVie, 1 North Waukegan Road, AP31-3, North Chicago, Illinois 60064, [2]Infectious Diseases, R48U, AP-30, AbbVie, 1 North Waukegan Road, North Chicago, Illinois 60064, [3]Department of Biometrics, AbbVie, 1 North Waukegan Road, AP31-2, North Chicago, Illinois 60064 and [4]Clinical Pharmacology and Pharmacometrics, AbbVie, 1 North Waukegan Road, R4PD AP31-3, North Chicago, IL 60064, USA

Keywords 3D regimen, direct-acting antiviral, HCV genotype 1, hepatitis C, paritaprevir

AIMS

Paritaprevir is a direct acting antiviral agent for use as part of a multidrug hepatitis C virus infection treatment regimen. To characterize the pharmacokinetics, safety, and tolerability of paritaprevir and determine an optimal dosing regimen for subsequent evaluations, clinical studies were conducted with paritaprevir alone or with ritonavir, a cytochrome P450 3A4 inhibitor anticipated to increase paritaprevir exposure.

METHODS

Two phase 1, double-blind, placebo-controlled, parallel group studies were conducted in healthy volunteers (NCT00850044 and NCT00931281). Single dose study participants (n = 87) were randomized to one time administration of either paritaprevir or placebo, or paritaprevir with ritonavir or placebo. Participants (n = 38) enrolled in the multiple dose study received paritaprevir with ritonavir or placebo once or twice daily for 14 days. Pharmacokinetics, safety and tolerability were assessed throughout the study treatment periods.

RESULTS

After single or multiple dose administration, paritaprevir displayed non-linear pharmacokinetics, with maximum plasma concentration and area under the plasma concentration–time curve increasing in a greater than dose proportional manner. Concomitant administration of 100 mg ritonavir increased paritaprevir exposure from a 300 mg dose approximately 30- to 50-fold and extended paritaprevir half-life. The tolerability of paritaprevir was similar with or without ritonavir. Asymptomatic, transient increases in bilirubin were observed but were not associated with abnormalities in other liver function tests.

CONCLUSIONS

Paritaprevir exhibits non-linear pharmacokinetics with greater than dose proportional increases in exposure after single or multiple dosing. Co-administration with ritonavir increases paritaprevir exposure and half-life without adversely influencing tolerability.

DOI:10.1111/bcp.12873

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Paritaprevir is a potent non-structural protein 3/4A protease inhibitor with antiviral activity against several hepatitis C virus (HCV) genotypes.
- Ritonavir, a strong inhibitor of cytochrome P450 3A4, is often used to augment HIV-1 protease inhibitor exposure.
- Co-administration with ritonavir could lower paritaprevir dosage and dosing frequency requirements.

WHAT THIS STUDY ADDS

- Paritaprevir exhibits non-linear pharmacokinetics after single or multiple dose administration.
- A 100 mg ritonavir dose extends paritaprevir's half-life and is optimal for enhancing paritaprevir exposure.
- At pharmacokinetic exposures substantially higher than those observed with approved HCV treatment, no safety signals of concern were observed for paritaprevir ± ritonavir.

Introduction

Chronic hepatitis C virus (HCV) infection affects approximately 2.8% of the world's population and is a leading cause of cirrhosis, end-stage liver disease and hepatocellular carcinoma [1]. Until recently, peginterferon and ribavirin were the standard of care for chronic HCV genotype 1 infection, which is the most prevalent HCV genotype worldwide, accounting for 76% of North American HCV cases and 59–89% of cases throughout Europe [1]. Due to the relatively low rates of sustained virologic response [2–4] and risks for toxicity associated with conventional peginterferon/ribavirin therapy [5], direct acting antiviral agents (DAAs) have replaced the combination of peginterferon and ribavirin as the preferred HCV treatment option. The most recent evolution in this therapeutic milieu is the introduction of DAA regimens that are interferon free, thus ameliorating the limitations associated with peginterferon use and broadening the population of subjects who are eligible for treatment.

Paritaprevir (also known as ABT-450) is a potent non-structural protein 3/4A protease inhibitor that was identified as a lead compound by AbbVie, Inc. (North Chicago, IL, USA) and Enanta Pharmaceuticals, Inc. (Watertown, MA, USA). Paritaprevir has demonstrated *in vitro* antiviral activity against several HCV genotypes, including 1a, 1b, 2a, 3a, 4a, and 6a [6]. Paritaprevir co-administered with ritonavir, ombitasvir and dasabuvir, referred to as the 3D regimen, has proven effective for the treatment of HCV genotype 1 infection and has been approved for this indication in the United States, Canada, and European Union, among others [7–12]. In definitive clinical trials, the 3D regimen plus ribavirin achieved sustained virologic response rates at 12 weeks after treatment (SVR12) of 92–100% in treatment-naïve and treatment-experienced non-cirrhotic subjects, and 93–100% after 24 weeks of treatment in subjects with cirrhosis, including previous null responders [8–12]. The 3D regimen was well tolerated in these trials, as demonstrated by low rates of treatment discontinuation and a generally mild adverse event profile [8–12]. Paritaprevir in combination with ritonavir and ombitasvir has also demonstrated efficacy in the treatment of HCV genotype 4 infection [13] and has been approved for this indication in Europe.

Ritonavir, a strong inhibitor of cytochrome P450 3A4 (CYP3A4), has long been used to increase circulating levels of HIV protease inhibitors used in antiretroviral therapy for HIV [14]. The primary metabolic enzyme for paritaprevir is CYP3A4 [15]. In the context of the 3D regimen, pharmacokinetic enhancement using ritonavir was initiated as a putative means to increase paritaprevir exposure, thus producing effective drug concentrations without need for higher doses or more frequent dose administration.

In this first characterization of paritaprevir pharmacokinetics in humans, various single- and multiple dose regimens were evaluated. In addition, the effect of ritonavir on the pharmacokinetics, safety and tolerability of paritaprevir was assessed. These studies provided the basis for further clinical evaluation of paritaprevir and the rationale for dosing regimens tested in subsequent clinical trials.

Methods

Participants

Men and women (post-menopausal or surgically sterile) aged 18–55 years with a body mass index between 18 and 29 kg m^{-2} and in general good health were eligible for study inclusion. Participants were excluded if they had tested positive for hepatitis A, B or C or were HIV positive, or had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels above the upper limit of normal on screening laboratory tests. Subjects were also excluded if they had used any medications, vitamins or herbal supplements within 2 weeks before study drug administration, had received any drug by injection within 30 days before study drug administration, had used known inhibitors or inducers of CYP3A within 1 month before study drug administration, had consumed alcohol within 48 h before study drug administration, had consumed star fruit, grapefruit or products with star fruit or grapefruit products within 72 h before study drug administration or had used tobacco or nicotine-containing products within 6 months preceding study drug administration. All study participants provided written informed consent.

Study design

Two phase 1, randomized, double-blind, placebo-controlled, parallel group studies with sequential designs were conducted (NCT00850044 and NCT00931281). Three groups of eight participants each were randomized in a 3 : 1 ratio to receive single ascending doses of paritaprevir or placebo and eight groups of eight participants each were randomized in a 3 : 1 ratio to receive single escalating doses of paritaprevir

in combination with ritonavir or to receive placebo. In the 14 day, multiple dose, dose escalation study, four groups of eight to 10 participants were randomized to receive paritaprevir with ritonavir or placebo once or twice daily. For all studies, dose escalation proceeded after evaluation of the safety, tolerability and pharmacokinetic data obtained from the preceding group.

In the single ascending dose study, the starting doses of paritaprevir of 300 mg alone and 25 mg with 100 mg ritonavir were based on the no-observed adverse effect level (NOAEL) dose from rat and dog toxicology studies. The NOAEL dose was used to estimate the human equivalent dose (HED) and a safety margin was applied to calculate the starting dose per regulatory guidance [*Guidance for Industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005, CDER*]. Doses were then escalated based on safety and pharmacokinetic data from previous doses. Doses in the multiple dose study were based on results from single dose administration.

Both studies were conducted in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki, and received approval from the Vista Medical Center East Institutional Review Board (IORG0005905).

Study drug treatments

All study drugs were administered orally under non-fasting conditions, with breakfast for once daily doses and with breakfast and an evening snack for twice daily doses, in the context of a standardized diet (30% fat, 40% carbohydrate, 1900 calories a day). In the single dose study, paritaprevir doses ranged from 25 to 900 mg and ritonavir doses ranged from 50 to 200 mg. Paritaprevir/ritonavir dose combinations studied were 25/100 mg, 100/50 mg, 100/100 mg, 100/200 mg, 200/75 mg, 300/100 mg, 400/50 mg and 400/100 mg. In the multiple dose study, participants received one of the following dose regimens for 14 days: placebo/placebo or paritaprevir/ritonavir 200/100 mg once daily, 100/100 mg twice daily, 50/100 mg twice daily or 300/100 mg once daily.

Assessments

Pharmacokinetics In the single dose study, blood samples for measuring paritaprevir and ritonavir concentrations were collected before dosing and then serially for 72 h after the dose (at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60 and 72 h). In the multiple dose study, blood samples for paritaprevir and ritonavir drug assays were collected on day 1 before the morning dose then serially for 15 h after dosing (at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 15 h). On day 14, blood samples for drug assays were collected before the morning dose and then serially for 72 h after the morning dose (at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 36, 48, 60 and 72 h). Trough samples were collected immediately before the morning dose on days 2, 3, 5, 7, 9 and 12.

Plasma concentrations of paritaprevir and ritonavir were determined using a validated salt-assisted liquid/liquid extraction liquid chromatography method with tandem mass spectrometric detection (HPLC-MS/MS). The HPLC column was a Waters Symmetry® C18 5 μm 2.1 x 50 mm column (Waters Corporation, Milford, MA, USA). The internal standards used in this assay were D_8-paritaprevir and D_5-ritonavir. The analysis required a sample volume of 100 μl plasma. The transition mass (m/z) for paritaprevir was 766➔571 and for ritonavir was 721➔296. The transitions (m/z) for the internal standards were 774➔ 571 for D_8-paritaprevir and 726➔296 for D_5-ritonavir. The lower limit of quantitation (LLOQ) for sample analysis of paritaprevir and ritonavir was established at 0.5 ng ml^{-1}. Each calibration contained eight standards ranging from approximately 0.5 ng ml^{-1} to 2050 ng ml^{-1} (single dose study) or 2070 ng ml^{-1} (multiple dose study) for paritaprevir and 5.0 ng ml^{-1} to 20 100 ng ml^{-1} (single dose study) or 24 600 ng ml^{-1} (multiple dose study) for ritonavir. In-study quality control (QC) samples were analyzed with the unknowns. The coefficient of variation (CV) values from the QCs for paritaprevir and ritonavir were less than or equal to 21.2% (single dose study) or 11.7% (multiple dose study), The mean bias values for undiluted QCs ranged from −3.4 to 7.3% (single dose study) or −1.9 to 4.1% (multiple dose study).

Safety Safety was assessed in both studies through periodic physical examinations, vital sign assessments, 12-lead electrocardiogram (ECG) measurements (performed at baseline, before dose, after each dose and at follow-up visits), serum chemistry and haematology tests and urinalysis. Participants were monitored for clinical and laboratory evidence of adverse events routinely throughout the study. Adverse events were evaluated for severity and relationship to study drug.

Pharmacokinetic analysis

In both studies, values for the pharmacokinetic parameters of paritaprevir and ritonavir were estimated using non-compartmental methods. The maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), concentrations at 12 h (C_{12}) and 24 h (C_{24}) and trough concentration before morning dose (C_{trough} for the multiple dose study) were taken directly from the plasma concentration–time data. Calculated pharmacokinetic parameters included the terminal phase elimination rate constant (λ_z) and half-life ($t_{1/2}$), area under the plasma concentration–time curve from zero to infinity (AUC(0,∞)) after a single dose and AUC from zero to τ (AUC(0,τ)), where τ is the dosing interval for multiple doses. An accumulation ratio (R_{ac}) for C_{max} and AUC(0,τ) in the multiple dose study was calculated as the ratio on day 14 to day 1.

Statistical analysis

Descriptive statistics were provided for demographic and safety parameters. Pharmacokinetic analyses were performed using dose-normalized, log-transformed C_{max}, AUC and C_{trough} values. Analysis of covariance for the pharmacokinetic variables of paritaprevir was used to investigate questions of dose proportionality and linear kinetics. In the multiple dose study, a repeated-measures analysis was used to assess the steady-state of paritaprevir C_{trough} using data from days 2 through 14. The effect of ritonavir on paritaprevir C_{max} and AUC was assessed by comparing the combination regimen of paritaprevir and ritonavir *vs*. the regimen of paritaprevir alone using the day 1 data from the single and multiple dose studies.

Results

Participant disposition and demographics

All enrolled participants (n = 87) completed the single dose study and the data from all participants were included in the analyses. In the multiple dose study, five of 38 enrolled participants prematurely discontinued the study, three due to adverse events (all receiving paritaprevir/ritonavir: one each in 200/100 mg once daily group, 100/100 mg twice daily group and 300/100 mg once daily group) and two withdrew consent to participate (one each receiving paritaprevir/ritonavir 200/100 mg once daily and placebo). Among the 30 participants randomized to active drug, 26 received paritaprevir/ritonavir throughout the study and were included in the pharmacokinetic analyses.

Baseline demographic characteristics, including mean age and weight, were generally comparable across treatment groups (Table 1). The study populations were predominantly male (67–94%) and most participants self-identified their race as White (50–83%).

Pharmacokinetics

Single dose study Increasing the paritaprevir dose from 300 to 900 mg increased drug exposure in a greater than dose proportional manner. Dose-normalized C_{max} and AUC(0,∞) values were significantly different in the 300, 600 and 900 mg dose groups ($P \leq 0.021$), ranging from 0.40 ± 0.23 to 5.7 ± 4.0 ng ml^{-1} mg^{-1} for C_{max} and 1.3 ± 0.6 to 9.7 ± 8.2 ng ml^{-1} h mg^{-1} for AUC(0,∞) (Table 2). Mean t_{max} and $t_{1/2}$, in contrast, were not appreciably influenced by dose. Plasma concentrations reached peak levels within 1.8–2.3 h and the mean $t_{1/2}$ was approximately 3 h, regardless of dose (Table 2).

Addition of ritonavir to paritaprevir markedly increased paritaprevir exposure (Figure 1). Compared with paritaprevir 300 mg administered alone, administration of paritaprevir 300 mg with ritonavir 100 mg increased mean paritaprevir C_{max} 28-fold, AUC(0,∞) 48-fold and C_{24} > 300-fold (Tables 2, 3). Additionally geometric mean ratios and 90% confidence intervals were determined from the single dose study as well as combined data from single and multiple doses to determine the effect of ritonavir on paritaprevir (Table 4).

The mean $t_{1/2}$ after a single dose of paritaprevir 300 mg increased from 2.7 h to 4.6 h when co-administered with ritonavir 100 mg and the t_{max} doubled (2.3–4.7 h, respectively).

As the paritaprevir dose increased from 25 to 400 mg in combination with ritonavir 100 mg, the paritaprevir C_{max} and AUC(0,∞) values increased in a greater than dose proportional manner (Table 3). The differences in mean dose-normalized C_{max} and AUC(0,∞) between paritaprevir/ritonavir 25/100 mg and 400/100 mg were approximately 60- and 50-fold, respectively. Paritaprevir t_{max} values, however, were not significantly different among the dose groups. The mean $t_{1/2}$ of paritaprevir generally decreased with paritaprevir dose increase, from 7.9 h for the 25/100 mg dose group to 4.9 h for the 400/100 mg dose group.

The influence of ritonavir dose increase on paritaprevir exposure was markedly less than that of paritaprevir dose increase. Paritaprevir AUC(0,∞) increased by approximately 200% with paritaprevir/ritonavir 100/100 mg relative to 100/50 mg, and by 65% with paritaprevir/ritonavir 100/200 mg compared with 100/100 mg (Table 3). The mean $t_{1/2}$ was generally consistent among groups with equivalent paritaprevir doses, although the paritaprevir t_{max} increased with ritonavir dose. This 65–200% increase in paritaprevir exposures with increasing ritonavir dose (100 *vs*. 50 mg or 200 *vs*. 100 mg) was significantly less than the 50- to 60-fold increase in paritaprevir exposures that were observed as paritaprevir dose increased from 25 mg to 400 mg once daily. Additionally, the 100 mg ritonavir dose was found to provide optimal enhancement of paritaprevir exposure without negatively impacting the safety profile.

Multiple dose study After multiple dosing, paritaprevir exposure increased in a greater than dose proportional manner

Table 1

Participant demographics (safety population)

	Single dose study				Multiple dose study	
	Without ritonavir		With ritonavir			
Parameter	**Placebo (n = 6)**	**Paritaprevir (n = 18)**	**Placebo (n = 16)**	**Paritaprevir + ritonavir (n = 47)**	**Placebo (n = 8)**	**Paritaprevir + ritonavir (n = 30)**
Age (years) mean (SD)	33.5 (5.3)	32.9 (11.2)	35.1 (12.0)	35.1 (10.2)	31.4 (12.1)	35.7 (9.8)
Gender, n (%)						
Female	2 (33)	1 (6)	4 (25)	10 (21)	1 (13)	4 (13)
Male	4 (67)	17 (94)	12 (75)	37 (79)	7 (88)	26 (87)
Race, n (%)						
White	5 (83)	12 (67)	10 (63)	30 (64)	4 (50)	23 (77)
Black or African American	1 (17)	5 (28)	5 (31)	16 (34)	3 (38)	5 (17)
Other	0	1 (6)	1 (6)	1 (2)	1 (13)	2 (7)
Weight (kg) mean (SD)	77.5 (12.1)	80.7 (8.1)	76.4 (11.2)	75.5 (9.3)	78.3 (8.7)	77.4 (10.9)

SD, standard deviation.

Table 2

Pharmacokinetic parameters (mean ± standard deviation) for paritaprevir after a single dose

Parameter	300 mg (*n* = 6)	600 mg (*n* = 6)	900 mg (*n* = 6)
C_{max} (ng ml^{-1})	120 ± 68	780 ± 600	5100 ± 3600
Dose-normalized C_{max} (ng ml^{-1} mg^{-1})	0.40 ± 0.23	1.3 ± 1.0	5.7 ± 4.0
t_{max} (h)	2.3 ± 0.5	1.8 ± 0.4	2.2 ± 0.4
AUC(0,∞) (ng ml^{-1} h)	390 ± 190	1700 ± 730	8800 ± 7400
Dose-normalized AUC(0,∞) (ng ml^{-1} h mg^{-1})	1.3 ± 0.6	2.8 ± 1.2	9.7 ± 8.2
C_{24} (ng ml^{-1})	0.13 ± 0.31	0.45 ± 0.51	0.99 ± 0.88
$t_{1/2}$ (h)*	2.7 ± 0.64	2.7 ± 1.2	3.1 ± 1.6

AUC(0,∞), area under the plasma concentration–time curve from zero to infinity; C_{24}, observed plasma concentration at 24 h; C_{max}, maximum observed plasma concentration; $t_{1/2}$, terminal phase elimination half-life; t_{max}, time to C_{max}. *Presented as the harmonic mean ± pseudo standard deviation.

(Figure 2). On day 14, dose-normalized paritaprevir C_{max} was approximately 3-fold higher and AUC(0,τ) was approximately 4-fold higher for the paritaprevir/ritonavir 300/100 mg once daily dose compared with the corresponding values for the 200/100 mg once daily dose ($P < 0.05$, Table 5). Paritaprevir exposures on day 14 were approximately 20–50% higher *vs*. day 1 exposures after once daily dosing, and 2- to 4-fold higher than day 1 exposures for twice daily dosing. The mean $t_{1/2}$ of paritaprevir was consistently within the range of 4–6 h, regardless of the dosing regimen.

Paritaprevir trough concentrations demonstrated an initial day-on-day increase through day 2 followed by a gradual decrease that stabilized by day 9 for once daily regimens and by day 12 for twice daily regimens (Figure 2). Results of the repeated-measures analysis performed to assess the attainment of paritaprevir steady-state based on C_{trough} data indicated that steady-state was reached after 7–12 days of dosing across the four doses and regimens.

Ritonavir pharmacokinetics Ritonavir C_{max} and AUC values increased with paritaprevir dose (Tables 6, 7). Among groups receiving a 100 mg ritonavir dose in the single dose study, a 16-fold increase in paritaprevir dose (25–400 mg) increased ritonavir AUC(0,∞) by 140%. Exposures with 100 mg ritonavir were substantially less than those with 200 mg ritonavir at any paritaprevir dose level. Results from the multiple dose study indicated minimal ritonavir accumulation with once daily dosing, and a 2.4- to 2.9-fold accumulation with twice daily dosing. The $t_{1/2}$ of ritonavir ranged from approximately 4–7 h.

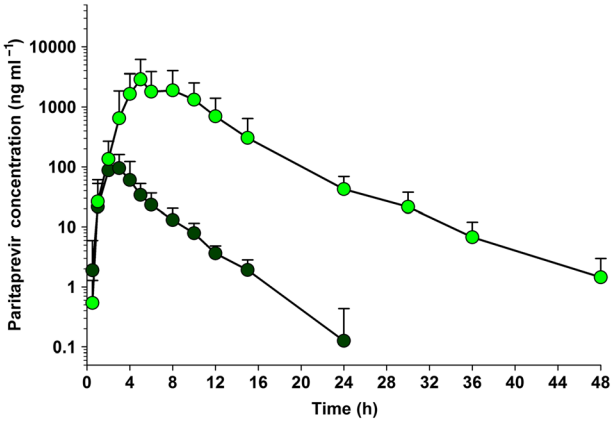

Figure 1

Mean plasma concentration–time profile after a single dose of paritaprevir 300 mg (paritaprevir 300 mg without ritonavir (*n*=6), paritaprevir 300 mg with ritonavir 100 mg (*n*=6)). Error bars represent standard deviations

Safety Paritaprevir with and without ritonavir was generally well tolerated in the 87 subjects in the single dose and multiple dose phase 1 studies. No serious adverse events occurred in either study. The most common adverse events in the single dose study were second degree atrioventricular block (demonstrated by a single dropped beat observed on telemetry monitoring), pyrexia and abdominal pain (Table 8). All reported cases of atrioventricular block were mild in severity and considered to be unrelated to study drug by the investigator. No clinically relevant changes in ECG were observed. Addition of ritonavir had no apparent effect on the tolerability profile of paritaprevir.

In the multiple dose study, the most common adverse events were fatigue, elevated bilirubin levels, headache and diarrhoea (Table 8). All events resolved by the end of the study follow-up period. The majority of events were classified as probably or possibly related to the study drug and as mild or moderate in severity by the investigator. Three participants prematurely discontinued from the study due to adverse events. Two were withdrawn because of elevated ALT levels (both <3 times the upper limit of normal [ULN]) and one was withdrawn because of increased blood bilirubin levels. The ALT increases were not associated with concomitant increases in bilirubin levels.

Among the eight participants in the multiple dose study who experienced an adverse event of increased blood bilirubin, five received paritaprevir/ritonavir 300/100 mg once daily, two received paritaprevir/ritonavir 100/100 mg twice daily and one received the 200/100 mg once daily. Total and indirect bilirubin values outside the normal range accounted for most cases of bilirubin elevation. Increased bilirubin levels were not accompanied by other liver function test abnormalities and normalized with continued drug dosing (Figure 3).

Table 3

Pharmacokinetic parameters (mean ± standard deviation) for paritaprevir after a single dose with ritonavir

Parameter	Paritaprevir + ritonavir dose group							
	25 mg + 100 mg (n = 5)	100 mg + 50 mg (n = 6)	100 mg + 100 mg (n = 6)	100 mg + 200 mg (n = 6)	200 mg + 75 mg (n = 6)	300 mg + 100 mg (n = 6)	400 mg + 50 mg (n = 6)	400 mg + 100 mg (n = 6)
C_{max} (ng ml^{-1})	10 ± 1.1	48 ± 29	120 ± 78	220 ± 170	1100 ± 1200	3400 ± 3300	7100 ± 5400	10 000 ± 5100
Dose-normalized C_{max} (ng ml^{-1} mg^{-1})	0.42 ± 0.04	0.48 ± 0.29	1.5 ± 0.78	2.2 ± 1.7	5.3 ± 5.8	11 ± 11	18 ± 14	26 ± 13
t_{max} (h)	4.0 ± 3.4	2.6 ± 1.5	4.2 ± 1.0	5.2 ± 1.9	3.5 ± 1.0	4.7 ± 2.1	3.2 ± 1.7	3.2 ± 1.2
AUC(0,∞) (ng ml^{-1} h)	100 ± 18	320 ± 85	970 ± 540	1600 ± 1200	5500 ± 5700	19 000 ± 18 000	44 000 ± 35 000	81 000 ± 62 000
Dose-normalized AUC(0,∞) (ng ml^{-1} h mg^{-1})	4.2 ± 0.72	3.2 ± 0.85	9.7 ± 5.4	16 ± 12	28 ± 29	62 ± 59	110 ± 88	200 ± 150
C_{24} (ng ml^{-1})	1.1 ± 0.45	2.8 ± 1.7	5.2 ± 2.2	9.3 ± 9.5	14 ± 9.2	43 ± 27	37 ± 36	430 ± 810
$t_{1/2}$ (h)*	7.9 ± 1.2	6.4 ± 2.7	5.7 ± 0.99	5.5 ± 0.80	4.8 ± 0.66	4.6 ± 1.2	4.0 ± 1.5	4.9 ± 0.93

AUC(0,∞), area under the plasma concentration–time curve from zero to infinity; C_{24}, observed plasma concentration at 24 h; C_{max}, maximum observed plasma concentration; $t_{1/2}$, terminal phase elimination half-life; t_{max}, time to C_{max}. *Presented as the harmonic mean ± pseudo standard deviation.

Table 4

Effect of 100 mg ritonavir on the exposures of 300 mg paritaprevir

Pharmacokinetic parameter	Geometric mean values 300 mg paritaprevir alone Single dose study	300 mg paritaprevir with 100 mg ritonavir Single dose study	Geometric mean ratio and 90% confidence interval
C_{max} (ng ml^{-1})	105	2030	19.3 (6.9 to 54.1)
AUC (ng ml^{-1} h)*	353	10 500	29.8 (10.1 to 87.7)
	Single dose study	Single and multiple dose study	
C_{max} (ng ml^{-1})†	105	3350	31.9 (13.2 to 77.4)
AUC (ng ml^{-1} h)*	353	18 000	50.9 (20.3 to 128.1)

*AUC(0,∞) for single dose and AUC(0,24 h) + C_{24}/λ_z on day 1 for multiple dose where λ_z is the terminal elimination rate constant following day 14 dose †C_{max} on day 1 for multiple dose

For both the single dose and multiple dose studies, there were no clinically significant changes from baseline in vital signs and no clinically significant QT_c prolongation was observed at any dose. Observed laboratory abnormalities were generally grade 1 (mild) in severity, transient and asymptomatic.

Discussion

Co-administration with ritonavir increases exposure of paritaprevir and prolongs its half-life. Additionally, after single or multiple dose administration with or without co-administration of ritonavir, paritaprevir displayed non-linear pharmacokinetics, with C_{max} and AUC increasing in a greater than dose proportional manner. Paritaprevir is a major substrate of CYP3A but not an inhibitor [15]. Paritaprevir is a substrate of efflux transporters (P-glycoprotein [P-gp] and breast cancer resistant protein [BCRP]) as well as liver uptake transporters (organic anion transporting polypeptide [OATP1B1 and OATP1B3]) [15–17]. The non-linearity of paritaprevir pharmacokinetics is likely due to the inhibition of efflux transporters in the gut and uptake transporters in the liver. In a similar manner, the increases in paritaprevir exposure attributable to ritonavir are ostensibly due to inhibition of CYP3A in both the intestine and the liver and efflux transporters, P-gp and BCRP primarily in the gut. Despite the supraproportional increases in exposure, minimal changes in paritaprevir half-life were observed with different doses or with single *vs.* multiple dose administration. However, co-administration with ritonavir increased the half-life of single dose paritaprevir from approximately 3 h to 5–8 h. The magnitude of increase in exposure in the presence of ritonavir (approximately 30-fold for C_{max} and 50-fold for AUC) allows for much lower doses of paritaprevir to be administered, while the much higher increase in C_{24} (>300-fold) allows for a lower frequency of dosing (once daily rather than twice daily).

In the multiple dose study, paritaprevir AUC(0,τ) on day 14 was approximately 20–50% higher after once daily dosing, and 2- to 4-fold higher after twice daily dosing compared with AUC(0,τ) values on day 1, which is indicative of limited accumulation. Steady-state was reached within 7–12 days of initiating

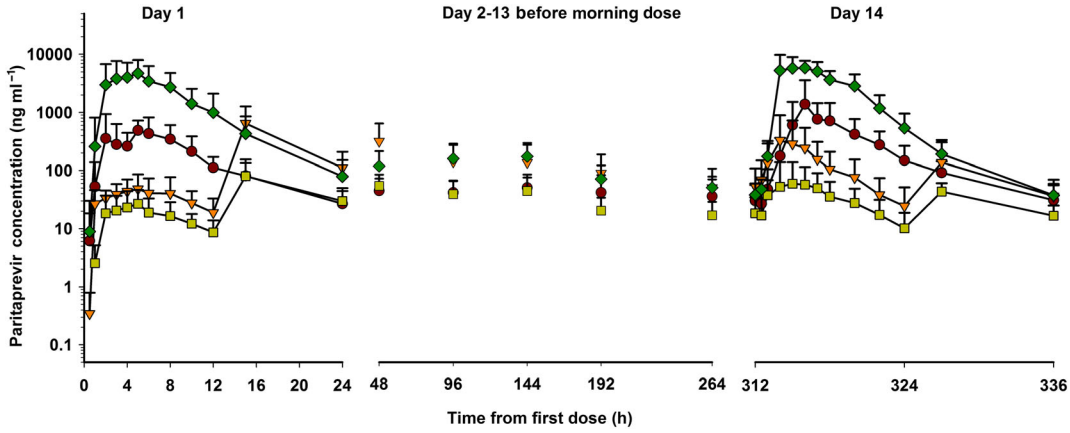

Figure 2

Mean plasma concentration–time profiles after multiple dose administration of paritaprevir with ritonavir once daily and twice daily regimens. Plasma concentrations were measured serially on day 1 and day 14. Trough samples were collected immediately before the morning study drug dose on days 2, 3, 5, 7, 9 and 12. Error bars represent standard deviations. 50/100 mg twice daily (*n*=8); 100/100 mg twice daily (*n*=70); 200/100 mg once daily (*n*=4); 300/100 mg once daily (*n*=7)

Table 5

Pharmacokinetic parameters (mean ± standard deviation) for paritaprevir after multiple doses with ritonavir

	Paritaprevir + ritonavir dose group							
	50 mg + 100 mg twice daily*		100 mg + 100 mg twice daily*		200 mg + 100 mg once daily		300 mg + 100 mg once daily	
Parameter	**Day 1 (*n* = 8)**	**Day 14 (*n* = 8)**	**Day 1 (*n* = 8)**	**Day 14 (*n* = 7)†**	**Day 1 (*n* = 6)**	**Day 14 (*n* = 4)†**	**Day 1 (*n* = 8)**	**Day 14 (*n* = 7)†**
C_{max} (ng ml^{-1})	29 ± 19	70 ± 84	52 ± 31	370 ± 540	660 ± 380	1500 ± 2100	6500 ± 3700	7300 ± 3000
Dose-normalized C_{max} (ng ml^{-1} mg^{-1})	0.57 ± 0.39	1.4 ± 1.7	0.52 ± 0.31	3.7 ± 5.4	3.3 ± 1.9	7.6 ± 11	22 ± 12	24 ± 10
t_{max} (h)	4.3 ± 0.9	4.1 ± 1.1	4.8 ± 2.7	3.1 ± 1.2	5.0 ± 2.0	4.8 ± 0.5	3.6 ± 1.2	3.4 ± 1.4
AUC(0,τ) (ng ml^{-1} h)	190 ± 130	410 ± 410	380 ± 240	1600 ± 2000	3900 ± 1600	6500 ± 6100	37 000 ± 23 000	38 000 ± 15 000
Dose-normalized AUC(0,τ) (ng ml^{-1} h mg^{-1})	3.7 ± 2.6	8.3 ± 8.3	3.8 ± 2.4	16 ± 20	19 ± 8.0	33 ± 31	120 ± 76	130 ± 50
$t_{1/2}$ (h)‡, §	—	4.9 ± 1.3	—	5.0 ± 0.48	—	5.7 ± 1.1	—	4.5 ± 0.74
R_{ac} C_{max}¶	—	1.89	—	3.83	—	1.16	—	1.53
R_{ac} AUC(0,τ)¶	—	1.91	—	2.79	—	1.23	—	1.49
C_{trough} (ng ml^{-1})	—	18 ± 16	—	54 ± 54	—	30 ± 26	—	38 ± 22

AUC(0,τ), area under the plasma concentration–time curve from zero to τ, where τ is the dosing interval for multiple doses; C_{max}, maximum observed plasma concentration; C_{trough}, observed plasma concentration prior to morning dose; R_{ac}, accumulation ratio; $t_{1/2}$, terminal phase elimination half-life; t_{max}, time to C_{max}. *Pharmacokinetic parameters after the morning dose. †Two participants in the 200 mg + 100 mg once daily group and one participant each in the 100 mg + 100 mg twice daily group and 300 mg + 100 mg once daily group discontinued prematurely and were not included in the analysis. ‡Harmonic mean ± pseudo standard deviation. §From day 14 afternoon dose. ¶Ratio of geometric mean C_{max} or AUC(0,τ) from study day 14 to study day 1 after the morning doses.

Table 6

Pharmacokinetic parameters (mean ± standard deviation) for ritonavir after a single dose of paritaprevir with ritonavir

Parameter	Paritaprevir + ritonavir dose							
	25 mg + 100 mg (*n* = 5)	100 mg + 50 mg(*n* = 6)	100 mg + 100 mg (*n* = 6)	100 mg + 200 mg (*n* = 6)	200 mg + 75 mg (*n* = 6)	300 mg + 100 mg (*n* = 6)	400 mg + 50 mg (*n* = 6)	400 mg + 100 mg (*n* = 6)
C_{max} (ng ml^{-1})	300 ± 170	90 ± 70	590 ± 310	2900 ± 1500	480 ± 330	670 ± 330	230 ± 220	1300 ± 940
t_{max} (h)	7.8 ± 2.3	5.6 ± 3.7	4.0 ± 1.5	5.7 ± 2.3	4.2 ± 1.2	7.2 ± 3.4	4.7 ± 3.1	4.3 ± 4.4
AUC(0,∞) (ng ml^{-1} h)	3900 ± 1800	780 ± 410	3600 ± 1400	23 000 + 12 000	3200 ± 1800	7000 ± 5800	1700 ± 1500	9300 ± 6600
$t_{1/2}$ (h)*	5.6 ± 1.1	6.5 ± 2.9	5.0 ± 0.45	5.4 ± 1.1	4.0 ± 1.0	4.0 ± 0.88	3.5 ± 1.3	3.5 ± 0.60

AUC(0,∞), area under the plasma concentration–time curve from zero to infinity; C_{max}, maximum observed plasma concentration; $t_{1/2}$, terminal phase elimination half-life; t_{max}, time to C_{max}. *Harmonic mean ± pseudo standard deviation.

Table 7

Pharmacokinetic parameters (mean ± standard deviation) for ritonavir after multiple doses of paritaprevir with ritonavir

Parameter	Paritaprevir + ritonavir dose							
	50 mg + 100 mg twice daily*		100 mg + 100 mg twice daily*		200 mg + 100 mg once daily		300 mg + 100 mg once daily	
	Day 1 (*n* = 8)	Day 14 (*n* = 8)	Day 1 (*n* = 8)	Day 14 (*n* = 7)†	Day 1 (*n* = 6)	Day 14 (*n* = 4)†	Day 1 (*n* = 7)	Day 14 (*n* = 7)†
C_{max} (ng ml^{-1})	560 ± 370	1200 ± 680	450 ± 200	1400 ± 800	790 ± 220	1300 ± 980	1100 ± 440	1000 ± 300
Dose-normalized C_{max} (ng ml^{-1} mg^{-1})	5.6 ± 3.7	12 ± 6.8	4.5 ± 2.0	14 ± 8.0	7.9 ± 2.2	13 ± 9.8	11 ± 4.4	10 ± 3.0
t_{max} (h)	5.6 ± 2.4	4.5 ± 1.4	6.4 ± 2.9	4.0 ± 3.2	5.7 ± 2.2	5.0 ± 0.8	4.5 ± 2.5	5.1 ± 1.3
AUC(0,τ) (ng ml^{-1} h)	2900 ± 2000	6700 ± 2800	2300 ± 1200	6500 ± 3500	6200 ± 2200	7900 ± 3600	7800 ± 3800	7500 ± 1800
Dose-normalized AUC(0,τ) (ng ml^{-1} h mg^{-1})	29 ± 20	67 ± 28	23 ± 12	65 ± 35	62 ± 22	79 ± 36	78 ± 38	75 ± 18
$t_{1/2}$ (h)‡, §	—	7.3 ± 2.8	—	4.9 ± 0.91	—	4.7 ± 0.71	—	3.6 ± 0.60
R_{ac} C_{max}¶	—	2.43	—	2.86	—	1.29	—	0.99
R_{ac} AUC¶	—	2.60	—	2.64	—	1.19	—	1.03

AUC(0,τ), area under the plasma concentration–time curve from zero to τ, where τ is the dosing interval for multiple doses; C_{max}, maximum observed plasma concentration; R_{ac}, accumulation ratio; $t_{1/2}$, terminal phase elimination half-life; t_{max}, time to C_{max}. *Pharmacokinetic parameters after the morning dose. †Two participants in the 200 mg + 100 mg once daily group and one participant each in the 100 mg + 100 mg twice daily group and 300 mg + 100 mg once daily group discontinued prematurely and were not included in the analysis. ‡Harmonic mean ± pseudo standard deviation. §From day 14 afternoon dose. ¶Ratio of geometric mean C_{max} or AUC(0,τ) from study day 14 to study day 1 after the morning doses.

Table 8

Treatment-emergent adverse events experienced by two or more participants during the treatment period (safety population)

Adverse event	Participants, *n* (%)					
	Single dose paritaprevir		Single dose paritaprevir + ritonavir		Multiple dose paritaprevir + ritonavir	
	Active (*n* = 18)	Placebo (*n* = 6)	Active (*n* = 47)	Placebo (*n* = 16)	Active (*n* = 30)	Placebo (*n* = 8)
Fatigue	0	0	0	0	8 (27)	0
Blood bilirubin increase	0	0	0	0	8 (27)	0
Headache	0	0	0	0	4 (13)	0
Diarrhoea	1 (6)	0	0	0	3 (10)	0
Abdominal pain	1 (6)	0	1 (2)	0	2 (7)	0
ALT increase	1 (6)	0	0	0	2 (7)	0
Muscle spasms	0	0	1 (2)	0	2 (7)	0
Presyncope	1 (6)	0	0	0	2 (7)	0
Atrioventricular block second degree	2 (11)	0	2 (4)	1 (6)	0	0
Pyrexia	0	0	2 (4)	0	0	0

paritaprevir/ritonavir treatment and was dependent on the dosing regimen. Paritaprevir trough concentrations stabilized after 9 days of consecutive once daily administration with ritonavir and after 12 days for twice daily regimens.

The 300/100 mg dose of paritaprevir/ritonavir was evaluated in both the single and the multiple dose studies and showed about a 2-fold difference in exposures after the initial dose. These inter-study differences are probably due to the high variability in paritaprevir pharmacokinetics. Inter-subject variability in paritaprevir exposure was higher as seen from the standard deviation associated with the C_{max} and AUC values. Paritaprevir exhibits non-linear pharmacokinetics which is believed to be due to the role of enzymes and transporters involved in paritaprevir disposition. The heterogeneity in expression of these enzymes/transporters could contribute to significant differences in exposure. Additionally, paritaprevir is co-administered with ritonavir, a drug with highly variable exposures. Since ritonavir significantly influences paritaprevir exposures by inhibiting some of these enzymes and transporters, variability in ritonavir exposure also affects paritaprevir.

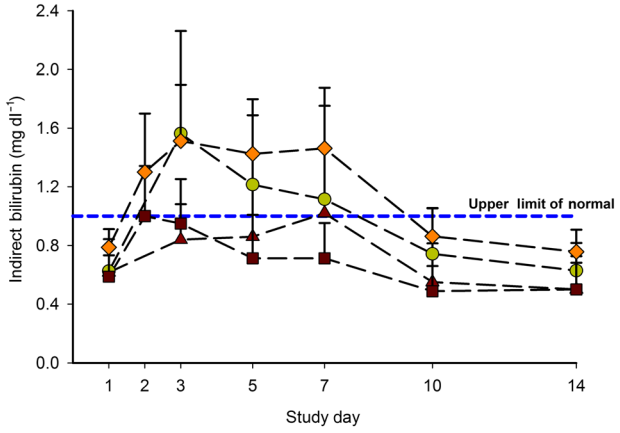

Figure 3

Mean indirect bilirubin measurement–time profiles after multiple dose administration of paritaprevir with ritonavir once daily and twice daily regimens. Error bars represent standard deviations (— ■ — paritaprevir/ritonavir 50/100 mg twice daily (*n*=8), — ● — paritaprevir/ritonavir 100/100 mg twice daily (*n*=7), — ▲ — paritaprevir/ritonavir 200/100 mg once daily (*n*=4), — ◆ — paritaprevir/ritonavir 300/100 mg once daily (*n*=7)

The effect of ritonavir on 100 mg paritaprevir was evaluated at three different ritonavir doses: 50, 100 and 200 mg. Paritaprevir AUC increased 3-fold when the ritonavir dose was doubled from 50 to 100 mg. Further doubling the ritonavir dose from 100 to 200 mg, however, increased the paritaprevir AUC less than 2-fold despite a 6.4-fold increase in ritonavir AUC. Alternately, increasing the paritaprevir dose from 100 to 300 mg (with ritonavir 100 mg) increased paritaprevir AUC approximately 20-fold. Thus, at doses greater than 100 mg ritonavir, increasing paritaprevir dose provides greater increases in exposures than increasing ritonavir dose. The 100 mg ritonavir dose is also the dose used as a pharmacokinetic enhancer for various HIV protease inhibitors. The 100 mg ritonavir dose allows co-dosing of the HIV protease inhibitors with the paritaprevir/ritonavir regimen. Hence, the ritonavir 100 mg dose is optimal for enhancing paritaprevir exposures.

Increases in ritonavir exposure were noted when co-administered with paritaprevir. The coefficient of variation for exposure variables (C_{max} and AUC) suggests that some of the observed between group differences may be the result of variability across dose groups. Any potential increase in ritonavir exposure due to paritaprevir is unlikely to be clinically significant, given that higher doses (and exposures) of ritonavir (200 mg) are routinely used to augment HIV protease inhibitor exposure without sequelae.

Adverse events experienced after administration of paritaprevir with or without ritonavir were generally mild and resolved during the course of the studies. A transient

increase in total bilirubin levels, primarily indirect, that occurred in the multiple dose study was the only adverse event that was more frequently observed in higher *vs*. lower dose groups. Most cases of bilirubin elevation occurred in the paritaprevir/ritonavir 300/100 mg once daily dose group and 100/100 mg twice daily dose group (200/200 mg total daily dose). In addition, for the same total daily dose of paritaprevir (100/100 mg twice daily *vs*. 200/100 mg once daily), increases in indirect bilirubin were higher with the twice daily regimen compared with the once daily regimen (Figure 3). These increases appear to be correlated with paritaprevir trough concentrations, as the once daily regimen had much higher C_{max} and AUC(0,τ) values but a lower C_{trough} for the same total daily dose of paritaprevir (Table 5).

The observed asymptomatic, transient increases in indirect bilirubin levels were not accompanied by increases in direct bilirubin or by other liver function test abnormalities. Even within the highest multiple dose treatment group (300/100 mg once daily), in which elevations in bilirubin levels were most prevalent, values normalized with continued drug administration (Figure 3). These observations mirrored those of paritaprevir clinical trials, wherein elevation of bilirubin levels was typically transient and not associated with elevations in serum ALT levels or other liver function test abnormalities [7–12, 18, 19]. Elevations in bilirubin levels are known to occur with drugs used in the treatment of HCV, including DAAs and ribavirin [20, 21]. The mechanism of transient elevation in bilirubin levels with paritaprevir is distinct from that of ribavirin, which induces haemolysis. It is believed that inhibition of OATP1B1 and OATP1B3 by paritaprevir [15, 17] affects bilirubin transport, thereby increasing circulating levels. Simeprevir, another DAA approved for treatment of HCV genotype 1 infection in combination with other antiviral agents, has also been associated with generally mild, transient elevations in bilirubin that have been attributed to its potent inhibition of the bilirubin transporter OATP1B1 [22].

There are several limitations that influence the interpretation of these results. The participants in the current analysis were healthy volunteers without HCV and hence any potential impact of HCV infection on the pharmacokinetics or tolerability of paritaprevir would not be detected in these studies. Safety conclusions are also limited by the duration of treatment, from a single dose to 14 days compared with the 12 to 24 week regimen that is used in the treatment of HCV. Despite these caveats, it is reassuring to note that the safety and tolerability results from phase 2 and 3 clinical trials were consistent with observations reported herein [7–12, 18, 19].

In conclusion, the results of these studies demonstrate that paritaprevir exhibits non-linear pharmacokinetics with greater than dose proportional increases in exposure after single or multiple dosing. Co-administration with ritonavir increases paritaprevir exposure and half-life without adversely influencing tolerability. A 100 mg ritonavir dose was found to be optimal for increasing paritaprevir exposure. The combination of paritaprevir with ritonavir was generally well tolerated in single and multiple doses for 14 days in the 87 healthy volunteers in the two phase 1 studies, even at doses greater than those used in the treatment of chronic HCV infection.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that the study was supported by AbbVie. RMM, CEK, TJP, Y-LC, SD, and WMA are employees of AbbVie and may hold AbbVie stocks or options.

The authors thank the AbbVie Clinical Pharmacology Unit, Victoria Mullaly, Jun Zhang and Karen Rynkiewicz for help with study conduct, sample analyses and data analyses and Angela Cimmino, PharmD and Crystal Murcia, PhD, of The JB Ashtin Group, Inc., for medical writing assistance in preparing this manuscript for publication. Editorial assistance was funded by AbbVie.

This work was sponsored by AbbVie. AbbVie contributed to the study design, research and interpretation of data, and the writing, reviewing and approving of the publication.

Contributors

Rajeev Menon contributed to study concept and design, analysis and interpretation of the data, and drafting and review of the manuscript. Cheri Klein, Thomas Podsadecki, Yi-Lin Chiu and Walid Awni contributed to study concept and design, interpretation of the data and review of the manuscript. Yi-Lin Chiu also performed statistical analyses. Sandeep Dutta contributed to the interpretation of study data, and drafting and review of the manuscript.

References

1 Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015; 61: 77–87.

2 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975–82.

3 Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM, Pegasys International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140: 346–55.

4 McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS, Ideal Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009; 361: 580–93.

5 Gentile I, Borgia F, Buonomo AR, Zappulo E, Castaldo G, Borgia G. ABT-450: a novel protease inhibitor for the treatment of hepatitis C virus infection. Curr Med Chem 2014; 21: 3261–70.

6 Pilot-Matias T, Tripathi R, Cohen D, Gaultier I, Dekhtyar T, Lu L, Reisch T, Irvin M, Hopkins T, Pithawalla R, Middleton T, Ng T,

McDaniel K, Or YS, Menon R, Kempf D, Molla A, Collins C. *In vitro* and *in vivo* antiviral activity and resistance profile of the hepatitis C virus NS3/4A protease inhibitor ABT-450. Antimicrob Agents Chemother 2015; 59: 988–97.

7 Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, Everson GT, Kwo P, Foster GR, Sulkowski MS, Xie W, Pilot-Matias T, Liossis G, Larsen L, Khatri A, Podsadecki T, Bernstein B. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med 2014; 370: 222–32.

8 Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, Mullhaupt B, Horsmans Y, Weiland O, Reesink HW, Rodrigues L Jr, Hu YB, Podsadecki T, Bernstein B. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced subjects with HCV genotype 1b infection. Gastroenterology 2014; 147: 359–65 e1.

9 Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, Weiland O, Aguilar H, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014; 370: 1594–603.

10 Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, Tam E, Marinho RT, Tsai N, Nyberg A, Box TD, Younes Z, Enayati P, Green S, Baruch Y, Bhandari BR, Caruntu FA, Sepe T, Chulanov V, Janczewska E, Rizzardini G, Gervain J, Planas R, Moreno C, Hassanein T, Xie W, King M, Podsadecki T, Reddy KR. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014; 370: 1983–92.

11 Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, Shiffman ML, Wedemeyer H, Berg T, Yoshida EM, Forns X, Lovell SS, Da Silva-Tillmann B, Collins CA, Campbell AL, Podsadecki T, Bernstein B. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014; 370: 1973–82.

12 Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, Sulkowski MS, Wedemeyer H, Tam E, Desmond P, Jensen DM, Di Bisceglie AM, Varunok P, Hassanein T, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014; 370: 1604–14.

13 Hezode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, Marcellin P, Hall C, Schnell G, Pilot-Matias T, Mobashery N, Redman R, Vilchez RA, Pol S. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced subjects with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet 2015; 385: 2502–9.

14 Hirsch MS, Gunthard HF, Schapiro JM, Brun-Vezinet F, Clotet B, Hammer SM, Johnson VA, Kuritzkes DR, Mellors JW, Pillay D, Yeni PG, Jacobsen DM, Richman DD. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an international AIDS society-USA panel. Clin Infect Dis 2008; 47: 266–85.

15 Bow DAJ, Liu J, Kavetskaia O, Menon R, de Morais SM, Nijsen M. A mechanistic non-clinical assessment of drug-drug interactions (metabolism and transporters) with the hepatitis C virus (HCV) regimen: ABT-450/r, ombitasvir and dasabuvir. In: AASLD/EASL Special Conference on Hepatitis C, New York, NY, 2014.

16 Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use. North Chicago, IL: AbbVie Inc., 2014.

17 Menon RM, Badri PS, Wang T, Polepally AR, Zha J, Khatri A, Wang H, Hu B, Coakley EP, Podsadecki TJ, Awni WM, Dutta S. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol 2015; 63: 20–9.

18 Lawitz E, Sullivan G, Rodriguez-Torres M, Bennett M, Poordad F, Kapoor M, Badri P, Campbell A, Rodrigues L Jr, Hu Y, Pilot-Matias T, Vilchez RA. Exploratory trial of ombitasvir and ABT-450/r with or without ribavirin for HCV genotype 1, 2, and 3 infection. J Infect 2015; 70: 197–205.

19 Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, Heckaman M, Larsen L, Menon R, Koev G, Tripathi R, Pilot-Matias T, Bernstein B. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med 2013; 368: 45–53.

20 Moreno-Monteagudo JA, Fernandez-Bermejo M, Garcia-Buey L, Sanz P, Iacono LO, Garcia-Monzon C, Borque MJ, Moreno-Otero R. Interferon alpha with ribavirin for the treatment of chronic hepatitis C in non-responders or relapsers to interferon monotherapy. Aliment Pharmacol Ther 1998; 12: 717–23.

21 Ridruejo E. Safety of direct-acting antivirals in the treatment of chronic hepatitis C. Expert Opin Drug Saf 2014; 13: 307–19.

22 Manns MP, Fried MW, Zeuzem S, Jacobson IM, Forns X, Poordad F, Peeters M, Fu M, Lenz O, Ouwerkerk-Mahadevan S, Jessner W, Scott JA, Kalmeijer R, De La Rosa G, Sinha R, Beumont-Mauviel M. Simeprevir with peginterferon/ribavirin for treatment of chronic hepatitis C virus genotype 1 infection: pooled safety analysis from phase IIb and III studies. J Viral Hepat 2015; 22: 366–75.